UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/759,207	01/16/2001	Iris Pecker	00/21505	1817

7590 04/08/2005

G. E. EHRLICH (1995) LTD.
c/o ANTHONY CASTORINA
SUITE 207
2001 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/759,207	PECKER ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 1/6/05 is acknowledged and has been entered.

Claims 26-37 are presently being examined.

The following are new grounds of rejection necessitated by Applicant's amendment filed 1/6/05.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 26-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed antibody specifically binding to or elicited by at least one epitope of a heparanase protein, said heparanase protein "being an active form" of a protein having an amino acid sequence as set forth at SEQ ID NO: 2 or at the SEQ ID NO: 2 Y246F variant.

The instant claims encompass antibodies to proteins that are specific for or elicited by heparanases comprising SEQ ID NO: 2 or the SEQ ID NO: 2 Y246F variant or by proteins of undisclosed structure that possess some activity that may or may not be endoglycosidase hydrolyzing activity. The said antibodies can be specific for or elicited by any "active form" of SEQ ID NO: 2 or the Y246F variant, i.e., it can be any substitution variant that has some undisclosed activity, or it can be any deletion or addition mutant or any undisclosed sequence that has some "activity". The recitation of "being an active form of a) or b)" recited in base claims 26 and 32 does not ensure that the "active form" of the SEQ ID NO recited in "a)" or "b)" has the same sequence as the said SEQ ID NO, nor that the "active form" has the endoglycosidase hydrolyzing activity. In addition, the instant claims that recite "elicited by at least one epitope" encompass antibodies that are elicited by a portion of the claimed heparanase protein, but that may

not bind specifically to the said heparanase protein, i.e., it is elicited towards an epitope not specific to the said heparanase. There is insufficient disclosure in the specification for said antibodies.

The specification discloses that anti-heparanase antibodies can be produced against heparanases that have widely disparate amino acid sequences, for example those cited on page 12 at lines 13-16 of the instant application, i.e., mouse B16-10 heparanase, human platelet heparanase, heparanases produced by several human tumor cell lines and CHO cells. The specification discloses (at the location cited by Applicant for support for "active form" on page 10 at lines 10-16) that two proteins found in melanoma that were thought to be heparanases lacked heparanase activity, i.e., endoglycosidase hydrolyzing activity, and were likely to be contaminants), and (on page 12 at lines 10-20) that polyclonal and monoclonal antibodies were raised against a purified, highly active, recombinant enzyme, they react with mouse B16-F10 heparanase, human platelet heparanases and heparanase enzymes produced by several human tumor cell lines and CHO cells, and that the said antibodies do not cross react with β-thromboglobulin, NAP-2, PAI-1 or bacterial heparinases I and III.

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as "being an active form of a) or b)" does not specifically define any of the compounds that fall within its definition, except for proteins comprising SEQ ID NO: 2 or the Y246F variant and having heparanase endoglycosidase hydrolyzing activity. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. In addition, a definition by function of "being an active form" where the activity is not specified and is not correlated with a specific structural feature, does not suffice to define the genus because it is only an indication of what the property the protein has, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

One of ordinary skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

4. Claims 26-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

The specification does not disclose how make and or/use claimed antibody specifically binding to or elicited by at least one epitope of a heparanase protein, said protein "being an active form of" SEQ ID NO: 2 or the Y246 variant.. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass antibodies that are specific for or elicited by proteins of undisclosed structure that possess some activity that may or may not be endoglycosidase hydrolyzing activity. The said antibodies can be specific for or elicited by any "active form" of SEQ ID NO: 2 or the Y246F variant, i.e., it can be any substitution variant that has some undisclosed activity, or it can be any deletion or addition mutant or any undisclosed sequence that has some "activity". The recitation of "being an active form of a) or b)" recited in base claims 26 and 32 does not ensure that the "active form" of the SEQ ID NO recited in "a)" or "b)" has the same sequence as the said SEQ ID NO, nor that the "active form" has the same activity. In addition, the instant claims that recite "elicited by at least one epitope" encompass antibodies that are elicited by a portion of the claimed heparanase protein, but that may not bind specifically to the said heparanase protein, i.e., it is elicited towards an epitope not specific to the said heparanase. There is insufficient disclosure in the specification for said antibodies.

The specification discloses that anti-heparanase antibodies can be produced against heparanases that have widely disparate amino acid sequences, for example those cited on page 12 at lines 13-16 of the instant application, i.e., mouse B16-10 heparanase, human platelet heparanase, heparanases produced by several human tumor cell lines and CHO cells. The specification discloses (at the location cited by Applicant for support for "active form" on page 10 at lines 10-16) that two proteins found in melanoma that were thought to be heparanases lacked heparanase activity, i.e., endoglycosidase hydrolyzing activity, and were likely to be contaminants), and (on page 12 at lines 10-20) that polyclonal and monoclonal antibodies were raised against a purified, highly active, recombinant enzyme, they react with mouse B16-F10 heparanase, human platelet heparanases and heparanase enzymes produced by several human tumor cell lines and CHO cells, and that the said antibodies do not cross react with β-thromboglobulin, NAP-2, PAI-1 or bacterial heparinases I and III.

There is no disclosure in the instant specification as to which amino acid residues at which positions comprise heparanase binding sites, which amino acid residues at other positions are tolerant of allowing the heparanase binding sites to function. The Examiner notes that Applicant presented examples in Appendix A of Applicant's amendment filed 5/27/03 for several heparanases of different sequence and the heparinase binding sites are not in the same position in the proteins and the said binding sites are not the same sequences.

The predictability of which changes can be tolerated in a polypeptide's amino acid sequence sand still retain function and properties requires a knowledge of, and guidance with regard to which amino acid residues at which positions in the amino acid sequence, if any are tolerant to modification and which are intolerant to modification, and detailed knowledge of the ways in which the product's structure relates to its function. Evidentiary reference Zhou et al (PNAS USA 1998, 95: 2492-7, of record) teaches that a single amino acid substitution in the HFE causes profound changes in the regulation of iron homeostasis in humans.

The literature reports numerous examples of structurally related polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al (U.S. Patent 5,194,596,of record) establishes that VGEF (a member of the PDGF family displaying a high degree of global homology with naturally occurring PDGF) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen in vivo, wherein endothelial pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125: 1591-1598; see Abstract and pp. 1594-1596, of record). In the transforming growth factor (TGF) family, Vukicevic et al (Proc. Natl. Acad. Sci. USA, Vol. 93, 1996, pages 9021-9026, of record) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- β family members BMP-2 and TGF- β 1 had no effect on metanephrogenesis under identical conditions (especially page 9023, paragraph bridging columns 1-2). See also Massague (of record), who reviews other members of the TGF- β family (1987, Cell 49: 437-8, especially p. 438, column 1, second full paragraph to the end). OP-1, BMP-2 and TGF- β 1 all display a high degree of global homology with one another. Similarly, PTH and PTHrP are two structurally related proteins that can have opposite effects on bone resorption (Pillbeam et al, Bone, Vol. 14, 1993, pages 717-720, especially page 717, second paragraph of Introduction, of record). Kopchick et al (U.S. Patent No. 5, 350, 836, of record) discloses several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid residue (column 2, lines 37-48).

Therefore, the problem of predicting functional aspects of the polypeptide product and what changes can be tolerated is complex and well outside the realm of routine experimentation.

There is insufficient guidance in the specification as to how to make and/or use the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 26-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 10-27 of U.S. Patent No. 6,562, 950 B2 in view of Hoogewerf et al (J. Biol. Chem. 270/7: 3268-3277, 1995, of record), U. S. Patent No. 5,206,223 (of record) and Bendig (METHODS: A Companion to Methods in Enzymology, 8: 83-93, 1995, of record).

The heparanase protein SEQ ID NO: 2 recited in the instant claims is 100% similar to SEQ ID NO: 1 recited in the claims of U.S. Patent No. 6,562, 950 B2, and the instant claims encompass the monoclonal antibody/pharmaceutical composition thereof claimed by U.S. Patent No. 6,562, 950 B2. Although the instant claims do not recite humanized or human monoclonal antibody, nor wherein the anti-heparanase antibody specifically inhibits heparanase activity, nor wherein the monoclonal antibody binds to a C-terminal portion of heparanase, Hoogwerf et al teach antibodies to the C-terminal portion of a putative heparanase protein was useful in inhibiting heparanase activity, U.S. Patent No. 5,206,223 discloses that inhibiting heparanase activity is useful for preventing or delaying allograft rejection or alleviating and treating an autoimmune disease such as arthritis, and Bendig teaches humanization of antibodies from non-human species such as rodents in order to reduce immunogenicity in humans. The

antibodies recited in the instant application as well as in U.S. Patent No. 6,562, 950 B2 are specific for human heparanase. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to humanize the antibody of the instant claims, to make the antibody against the C-terminal portion of the heparanase, and to make a neutralizing antibody. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to inhibit heparanase activity in humans.

7. Claims 26-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 U.S. Patent No. 6,177,545 B1.

The said claims of U.S. Patent No. 6,177,545 B1 are drawn to polyclonal and monoclonal antibodies specifically binding to or elicited by heparanase protein having the amino acid sequence set forth at SEQ ID NO: 2.

Instant claims 31 and 37 are included in this rejection because heparanase has the enzyme activity recited in the said claims.

8. Claims 26-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 22-34, 59-63, 80-92, 114, 131-133, 189-194, 341-345, 351-353, 355-359 and 365-367 of copending Application No. 10/645,659 in view of U. S. Patent No. 5,206,223 (of record), Bendig (METHODS: A Companion to Methods in Enzymology, 8: 83-93, 1995, of record) and U.S. Patent No. 4,946,778.

The heparanase protein SEQ ID NO: 2 Y246F variant recited in the instant claims is 100% similar to SEQ ID NO: 4 recited in the claims of copending Application No. 10/645,659, and the instant claims encompass the monoclonal antibody/pharmaceutical composition thereof claimed by copending Application No. 10/645,659. Although the instant claims do not recite humanized monoclonal antibody, U.S. Patent No. 5,206,223 discloses that inhibiting heparanase activity is useful for preventing or delaying allograft rejection or alleviating and treating an autoimmune disease such as arthritis, and Bendig teaches humanization of antibodies from non-human species such as rodents in order to reduce immunogenicity in humans. The antibodies recited in the instant application as well as in copending Application No. 10/645,659 are specific for human heparanase. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to humanize the antibody of the instant claims and to have administered it in a pharmaceutical composition. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to inhibit heparanase activity in humans. Although the instant claims do not recite chimeric, Fab, single chain, immunobilized or labeled monoclonal antibody, these are obvious variants of the anti-heparanase antibodies, and they are encompassed by the instant claims. In addition, U.S. Patent No. 4,946,778 discloses the advantages of using single chain antibodies, the use of Fab fragments of antibodies, and that antibodies may be

immunobilized or detectably labeled for ultilization in diagnostics, therapy, in *in vivo* or *in vitro* imaging, purifications and biosensors (especially columns 1-3). With respect to the recited homology percentages, the antibodies recited in copending Application No. 10/645,659 are also "active forms" of the SEQ ID NO: 2 Y246F variant recited in the instant claims, and so the instant claims encompass them. The instant claims do not recite the specific monoclonal antibodies recited for example in claim 353 of copending Application No. 10/645,659, but they are encompassed by the instant claims because they are anti-heparanase monoclonal antibodies.

This is a provisional obviousness-type double patenting rejection.

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
March 24, 2005

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600